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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,889	01/19/2001	Rosalie Luiten	L0461/7104	9782

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/766,889	LUITEN ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8 and 79-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 79-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. Applicant's amendment filed 12/23/04 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election without traverse of Group I (claims 8 and 79-85) in Applicant's response filed 6/7/04.

The following are new grounds of rejection necessitated by Applicant's amendment filed 12/23/04.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 8 and 81-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed method for stimulating an immune response comprising administering an HLA-B35 binding peptide comprising SEQ ID NO: 10 that is not SEQ ID NO: 8 or 9, nor one comprising SEQ ID NO: 8, 9 or 10 that is not a subsequence of SEQ ID NO: 2.

The instant claims encompass a method of using a peptide comprising SEQ ID NO: 10 that may be up to any length for binding HLA-B35 and that is not a subsequence of SEQ ID NO: 2 for stimulating an immune response in an HLA-B35 positive subject wherein the immune response is specific for the HLA-B35 binding peptide, but not necessarily in context of restriction by HLA-B35.

The specification does not disclose peptides comprising SEQ ID NO: 10 (ADPTGHSY) that are not subsequences of SEQ ID NO: 2 (MAGE-A1 protein sequence), i.e., that are not one of SEQ ID NO: 8 (EADPTGHSY), SEQ ID NO: 9 (KEADPTGHSY), or SEQ ID NO: 5 (EADPTGHSYVLV) that are recognized by HLA-B35-restricted CTL.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 8 and 79-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 recites the limitation "or the complex" at the last line. There is insufficient antecedent basis for this limitation in the claim, as the limitation "a complex" recited in the previous version of the claim has been deleted in Applicant's amendment filed 12/23/04.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 8 and 79-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,667,037 B1 in view of WO 95/04542, Rammensee et al (Immunogenetics, 1995, 41: 178-228, IDS reference), Rammensee et al (MHC Ligands and Peptide Motifs, 1997, pages 263-265, of record) and admitted prior art in the specification on pages 62-63 at the sentence spanning the said pages.

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater

With regard to instant base claim 8, the claimed method recites stimulating an immune response in an HLA-B35 positive subject, comprising administering a MAGE-A1 HLA-B35 binding peptide comprising SEQ ID NO: 10 (i.e., ADPTGHSY) in an amount sufficient to stimulate an immune response specific for the said peptide. The claims are being interpreted to include stimulating an immune response in an HLA-B35 positive subject comprising administering the said peptide in an amount sufficient to stimulate an immune response specific for the said peptide, not necessarily in context of HLA-B35.

The instant specification discloses at a variety of locations (for example, on page 62 at lines 23-26) that the peptide EADPTGHSY is capable of stimulating both HLA-A1 and HLA-B35 restricted MAGE-1 specific CTL, or of eliciting a humoral response.

U.S. Patent No. 6,667,037 B1 discloses the MAGE-1 antigenic peptide EADPTGHSY (SEQ ID NO: 8 of the instant claims and an HLA-B35 binding peptide comprising SEQ ID NO: 10 of the instant claims) restricted by HLA-A1 and testing of complexes of HLA/β2m in combination with this peptide for identification or isolation of CTL (especially column 6 at line 26). U.S. Patent No. 6,667,037 B1 further discloses peptides (TAAs, tumor rejection antigens) that bind to HLA-B35 from the melanoma TRAP tyrosinase can be administered to HLA-B35 positive patients to induce a CTL response, and further that they can be administered in combination together, or as polytope constructs along with peptides from other TRAPs and with MHC class II restricted peptides, i.e., Th epitopes, and the compositions may include adjuvants such as the cytokines IL-6 or IL-12 (especially abstract, paragraph spanning columns 4 and 5, sentence spanning columns 6 and 7, columns 7 and 8). U.S. Patent No. 6,667,037 B1 discloses that it is known that individuals generally express six different HLA molecules on their cell surfaces (especially column 4 at lines 63-64). U.S. Patent No. 6,667,037 B1 discloses that a CTL line CTL 35-24 recognized a tyrosinase peptide presented on the surface of target cells expressing HLA-A24, HLA-B35, HLA-B44 and HLA-Cw*04 in context of HLA-B*3503 .

U.S. Patent No. 6,667,037 B1 does not disclose wherein the TAAs from tyrosinase are administered along with a peptide comprising EADPTGHSY in a composition that includes cytokines, nor wherein the said peptide is administered to an HLA-B35 positive subject and induces an immune response specific for the peptide.

WO 95/04542 teaches that MAGE-1 is a melanoma TRAP that contains TAA peptides that can be combined in a cocktail to provide enhanced immunogenicity for CTL or Th-mediated responses and administered to patients, and that the cocktail may include universal Th epitopes (especially page 12, Abstract). WO 95/04542 teaches that the peptides of one region of a TRAP can be combined with peptides having different MHC restriction elements in order to effectively broaden the immunological coverage provided by therapeutic, vaccine or diagnostic compositions among a diverse population, and that HLA-A1 binding peptides are useful in such compositions (especially page 12 at lines 5-23).

Rammensee et al (Immunogenetics) teach that the motif for peptides that bind to HLA-B3501 is P2 Pro and P9 Tyr, whereas the motif for peptides that bind to HLA-A1 is Asp or Glu at position 3 and Tyr at P9, i.e., that the peptides that bind to each have a common P9 anchor residue. Rammensee et al further teach preferred residues at non-anchor positions. Rammensee et al teach the peptide EADPTGHSY is a T cell epitope from MAGE-1 that binds to HLA-A1.

Rammensee et al (MHC Ligands and Peptide Motifs) teach that preferred residues for peptides that bind to HLA-B3501 include A at the P2 anchor position, and P at the P4 and T at the P5 non-anchor positions (as does EADPTGHSY) and that a T cell epitope peptide from HIV env protein (TAVPWNASW) containing no primary anchor residue amino acid residues, has the preferred residues A at the P2 anchor position, P at the P4 non-anchor position and S at the P8 non-anchor position (as does E**A**D**PT**GH**S**Y) (pages 263-265).

The admitted prior art in the specification on pages 62-63 at the sentence spanning the said pages is that Pagupathi et al teach that at least 27 different HLA-B35 alleles have been identified, and that HLA-B3501 and HLA-B3503 have 12% frequency.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the MAGE-1 antigenic peptide EADPTGHSY restricted by HLA-A1 disclosed by U.S. Patent No. 6,667,037 B1 and by Rammensee et al in the composition of U.S. Patent No. 6,667,037 B1 with the HLA-B35 binding peptide(s) disclosed by U.S. Patent No. 6,667,037 B1 since: (1) U.S. Patent No. 6,667,037 B1 discloses combining tyrosinase TAA peptides with peptides from other TRAPS and that MAGE-A1 is a TRAP, (2) WO 95/04542 teaches that the peptides of one region of a TRAP can be combined with peptides having different MHC restriction elements in order to effectively broaden the immunological coverage provided by therapeutic, vaccine or diagnostic compositions among a diverse population and that HLA-A1 binding peptides are useful in such compositions, (3) Rammensee et al teach anchor residues for peptides that bind to both HLA molecules, and (4) the admitted prior art is that HLA-B35 alleles have a high frequency in the population, as does HLA-A1, as was recognized by one of skill in the art at the time the invention was made. It would also have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the MAGE-1 antigenic peptide EADPTGHSY restricted by HLA-A1 disclosed by U.S. Patent No. 6,667,037 B1 and Rammensee et al in the composition of U.S. Patent No. 6,667,037 B1 with the HLA-B35 binding peptide(s) disclosed by U.S. Patent No. 6,667,037 B1 because one of ordinary skill in the art at the time the invention was made would have realized that the MAGE-1 peptide might also bind to HLA-B53 since Rammensee et al (both references) teach anchor residue and preferred residue motifs for peptides that bind to HLA-A1 and to HLA-B35 include a common P9 anchor residue of "Y" as does EADPTGHSY, and since Rammensee et al (MHC Ligands and Peptide Motifs) teach that E**A**D**PT**GH**S**Y has preferred residues at the anchor and non-anchor positions (bolded and underlined) and that an antigenic peptide that binds to HLA-B35 lacked optimal anchor residue amino acids or had non-preferred amino acid residues at the anchor positions, but had preferred amino acid residues at anchor or non-anchor positions.

One of ordinary skill in the art would have been motivated to do this in order to make a composition comprising HLA-B35 and HLA-A1 binding antigenic peptides for use in a therapeutic composition such as that taught by the combination of U.S. Patent No. 6,667,037 B1 and WO 95/04542 to provide coverage of more than one frequent MHC class I allele in a diverse population for more than one melanoma specific antigen, i.e., tyrosinase and MAGE-1 using peptides taught by U.S. Patent No. 6,667,037 B1 and Rammensee et al, the said diverse population including an individual possessing HLA-B35.

It is an expected property of the EADPTGHSY peptide that it would stimulate an either a humoral or a cellular (i.e., CTL) immune response in an HLA-B35 positive subject who also was positive for HLA-A1, the immune response being restricted by HLA-A1 and/or HLA-B35.

Applicant's arguments in the amendment filed 12/23/04 have been fully considered but are not persuasive.

Applicant's position is of record in the said amendment on pages 8-10, briefly that : (1) '037 does not disclose that the peptide EADPTGHSY is presented by HLA-B35, nor a method for stimulating an immune response as recited in the instant claims, (2) although '037 discloses that tyrosinase can be processed to produce a peptide that is presented by HLA-B35, the disclosure does not provide motivation to look at other proteins as encoding HLA-B35 presented peptides such as those from MAGE-1, and that the said tyrosinase peptide has a different sequence from the peptide recited in the instant claims, (3) '037 teaches away from the present invention because one of ordinary skill in the art would be left with the impression that MAGE-A1 was tested and that it did not encode the peptide presented by HLA-B35 and recognized by CTL 35-24, that the peptides in column 6 would not be expected to bind to HLA-B35 because of contrary experimental evidence in example 2, (4) that in the Celis reference cited by the Examiner in the enablement rejection (in the previous office action) illustrates the point that there is not a reasonable expectation of success based upon computer-based prediction of peptide epitopes absent experimental confirmation, (5) none of the other references supply the missing motivation or elements.

It is noted by the Examiner that U.S. Patent No. 6,667,037 B1 does not disclose using any other cell line to test for reactivity to other melanoma proteins/peptides or to any other HLA restriction elements present on the target cell, including HLA-B35 restricted MAGE-1 peptides. It is therefore, the Examiner's position that the '037 patent discloses use of only one CTL, i.e., CTL 35-24, which would necessarily be restricted to one HLA molecule and a peptide from one melanoma protein, to identify which protein and peptide and restriction element from the 4 comprising the haplotype of the presenting cell was the relevant ones for that particular CTL, as enunciated in the instant rejection supra. It is the Examiner's further position that because of this, '037 does not teach away from the present invention because one of ordinary skill in the art at the time the invention was made would have realized that only one CTL was tested and that that did not preclude that other peptides from other proteins could be presented by HLA molecules. It is the Examiner's position that example 2 of '037 discloses use of the Rammensee et al 1995 motif for HLA-B*3501 (in the absence of knowing one for HLA-B*3503) was P2 Pro and P9 Tyr, and as enunciated supra in the instant rejection for peptides that bind to HLA-B*3501; however, the instant rejection also includes the Rammensee 1997 extended motif for HLA-B*3501, that being the disclosure of preferred residue Ala at the P2 anchor position, Tyr at the P9 position, and preferred residues Pro at the P4/Thr at the P5 non-anchor positions, (4) that the Celis et al reference was relied upon for the teaching that although experimental ranking schemes are available for predicting relative binding strengths of some HLA binding nonapeptides, and assays are available to test the binding of peptides to HLA, an undue amount of experimentation would be involved in determining peptides from the many possibilities [of functional variants of the fully defined peptides SEQ ID NO: 8, 9, 5, or 10, or those comprising these peptides recited in the instant claims] that would be capable of binding to HLA and inducing a CTL response, i.e, of designing peptides that would not necessarily be substitution variants of the fully defined peptides, but rather, functional variants that would encompass totally different sequences. In addition, it is the Examiner's position that Rammensee et al (1997) teach a CTL epitope (TAVPWNASW) that has no primary anchor residues but that has preferred amino acid residues at the P2 anchor position and at the P4 and P5 non-anchor positions in the absence of a P9 Tyr anchor residue, that this peptide binds to HLA-B*3501 and elicits CTL. It is the Examiner's position that the E**A**DP**T**GHS**Y** peptide has the preferred A at P2 anchor position as does the Rammensee et al HIV peptide, has preferred amino acid residues at position 4 as does the Rammensee et al peptide, and contains the P9 Tyr anchor amino acid residue and a preferred P4 amino acid residue unlike the Rammensee et al peptide, so there would be a reasonable expectation that the EADPTGHSY peptide would bind to HLA-B35 with high enough affinity to elicit an immune response, and one of ordinary skill in the art at the time the invention was made would have been motivated to administer the peptide to patients who were both HLA-A1 and HLA-B35 positive, and to administer the peptide in a cocktail or combined in a polytope to a population of patients targeted for expressing HLA class I alleles of high frequency such as HLA-A1 and HLA-B35, because the peptide would be capable of

stimulating an immune response specific for the EADPTGHSY peptide in context of HLA-A1 (the instant claims do not recite that the response must be HLA-B35 restricted).

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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